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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,584	03/12/2001	Matthew L. Albert	600-1-276 CIP	5033

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,584	ALBERT ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *5-14,20 and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,15-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action..

Acknowledgement is made of applicants claim to the priory documents of 60/075,356, filed February 20, 1998, 60/077,095, filed March 6, 1998 and 60/101,749, filed September 24, 1998. After review and reconsideration of these provisional application it is concluded that they do not provide adequate written description for the instant invention. 60/075,356 and 60/077,095, although providing a written description of cross presentation of antigens via dendritic cells which are exposed to apoptotic cells having said antigen, makes o reference to a method of inducing tolerance to said antigen by exposing the dendritic cells to apoptotic cells without helper T-cells. 60/101,749 briefly ,mentions that tolerance can be induced by exposing dendritic cells to apoptotic cells in the absence of T helper cells as in the method of Steinman (Immunol Rev 1997, Vol. 156, pp. 25-37). Upon consulting the cited paper it is noted that Steinman contemplates a specialized resident population of dendritic cells within the T-cell areas that express high levels of self-antigen and functional fas ligands capable of inducing CD+4 T cell death (abstract). Steinman speculates that "a lack of CD+4 helper T cells may in turn be pivotal for maintaining the silence of those self-reactive B cells and CD8= killer cells that escape central deletion in the marrow or the thymus". However, none of the provisional applications provide adequate written description of a method wherein T-cell help is eliminated by methods other than the simple exclusion of T-helper cells from the dendritic cells in the presence of the apoptotic cells. Further, application number 09/251,896 also does not describe methods for induce tolerance by elimination of effective T-cell help by the instant methods. Accordingly, the instant invention will be given the effective priority date of the 09/565,958 application, May 5, 2000.

Claims 1-41 are pending. Claims 23-41, drawn to non-elected inventions are withdrawn from consideration. Claims 5-14 and 20, drawn to non-elected species are also withdrawn from consideration. Claims 1-4, 15-19, 21 and 22 are under consideration.

The rejection of claims 1, 2, 4, 15, 16, 17, 19, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) in view of Migita et al (Journal of Clinical Investigation, 1995, Vol. 96, pp. 727-732) and Banchereau et al (Nature, 1998, Vol. 392, pp. 245-252) and Guibinga et al (Journal of Virology, 1998, vol. 72, pp. 4601-46090. is re-made for reasons of record

Claim 1 is drawn to a method for inducing tolerance in a mammal to an antigen comprising the steps of isolating peripheral blood mononuclear cells from said mammal; isolating dendritic cells from said peripheral blood mononuclear cells; exposing said dendritic cells ex vivo to apoptotic cells expressing said antigen in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+T cell help; introducing a cellular portion of step (c) into said mammal; wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said mammal resulting in tolerance to said antigen. claim 2 embodies the method of claim 1 wherein dendritic cell maturation molecule is selected from the group consisting of PGE2, TNF-alpha, LPS, monocyte conditioned medium, CpG-DNA or any combination thereof. Claim 4 embodies the method if claim 1 wherein said absence of effective CD4+ T-cell help is achieved by including in step (c) at least one agent that inhibits or eliminates effective CD4+ T cell help. Claim 15 embodies the method of claim 4 wherein said agent inhibits signaling consequent to dendritic-cell CD4 T cell engagement. Claim 16 embodies the method of claim 15 wherein said agent is a FKBP antagonist. Claim 17 specifies that the FKBP antagonist is FK506. Claim 19 embodies the method of claim 1 wherein said antigen is a viral antigen. Claim 21 embodies the method of claim 1 wherein the infusion of the cellular portion of step (c) is done after a period of time. Claim 22 embodies the method of claim 1 wherein said mammal is human.

Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) teach that apoptotic cells are phagocytosed by dendritic cells. Rovere et al teach that dendritic cells control there own maturation by selectively releasing maturation factors when challenged with a relative excess of dendritic cells. (Page 4470, first column, lines 5-8). Rovere et al point out that dendritic cells secrete substantial amounts of TNF-alpha when challenged with high numbers of apoptotic cells(page 4469, second column, lines 5-7 of the first full paragraph), thus fulfilling the specific embodiment of claim 2 drawn to TNF-alpha as a dendritic cell maturation factor. .

Banchereau et al (Nature, 1998, Vol. 392, pp. 245-252) teach that dendritic cells are involved in the induction of peripheral tolerance versus central tolerance (page 250, first column, third paragraph under the heading "Dendritic cells and T-cell tolerance").

Migita et al (Journal of clinical Investigation, 1995, Vol. 96, pp. 727-732) teach that FK506 exclusively induced apoptosis of antigen-stimulated T-cells (page 731, first column, lines 11-16 of the first full paragraph, and second column, first paragraph).

Guibinga et al (Journal of Virology, 1998, vol. 72, pp. 4601-4609) teach that FK506 in combination with CTLA4Ig abrogated the immune response against adenovirus proteins. Guibinga et al teach that CD+8 lymphocytes which destroy adenovirus infected cells counter the beneficial effects of adenovirus mediated gene therapy, and that the elimination of the immune response against the adenovirus was necessary in the treatment of genetic diseases which would require long-term transgene expression and repeated vector delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to induce tolerance to the adenovirus by means of contacting peripheral blood dendritic cell with apoptotic cells which have been infected with the adenovirus; growing the dendritic cells until they mature; administering said mature dendritic cells to a human in need of adenovirus mediated gene therapy in addition to FK-506 and CTLA4Ig, wherein CD+8 cells which are activated by said dendritic cells will undergo apoptosis resulting in tolerance to said adenovirus antigens. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rovere et al on the cross presentation of antigens by means of phagocytosis of apoptotic cells by dendritic cells; the teaching of Banchereau et al on the mediation of peripheral tolerance by dendritic cells; the teachings of Migita et al on the specific induction of apoptosis by FK506 in activated versus resting T cells and the teachings of Guibinga et al on the abrogation of the CTL immune response against adenovirus antigen by the administration of FK506 and CTLA4Ig to mice. Further the administration of FK506 would inherently comprise the claimed properties of being a FKBP antagonist, and inhibiting or eliminating effective T-cell help consequent to dendritic-cell CD4 T-cell engagement.

It is noted that none of the provisional applications provide a written description of FK506 as an agent which inhibits CD4 T-cell signaling consequent to dendritic cell CD+4

engagement, nor is there any written description of a method which utilizes agents which inhibit effective CD4 T cell help as opposed to the physical elimination of CD+4 T cells.

The rejection of claims 1, 2, 4, 15-19, 21 and 22 under 35 U.S.C. 103(a) as being unpatentable over Rovere et al (Journal of Immunology, 1998, Vol. 161, pp. 4467-4471) and Migita et al (Journal of clinical Investigation, 1995, Vol. 96, pp. 727-732) and Banchereau et al (Nature, 1998, Vol. 392, pp. 245-252) and Guibinga et al (Journal of Virology, 1998, vol. 72, pp. 4601-4609) as applied to claims 1, 4, 15, 16, 17, 19, 21 and 22 above, and further in view of Li et al (Transplantation, 1998, Vol. 66, pp. 1387-1388) and Sehgal (Clinical biochemistry, 1998, Vol. 31, pp. 335-340) is re-made for reasons of record.

The embodiments of claims 1, 4, 15-19 21 and 22 are set forth above. Claim 18 embodies the method of claim 16 wherein said TOR antagonist is rapamycin. The combination of Rovere et al and Migita et al and Banchereau et al and Guibinga et al render obvious claims 1, 4, 15, 16, 17, 19, 21 and 22 for the reasons set forth above. Neither of the aforesaid references teach rapamycin for the inhibition or elimination of effective CD4+ T cell help consequent to dendritic cell-CD4 T cell engagement or by means of a TOR antagonist.

Li et al teach that CTLA4Ig combined with rapamycin results in a permanent tolerization to a tissue engraftment. Li et al teach that rapamycin blocks Il-2 induced proliferative but not apoptotic signals is required to achieve tolerance to an antigen (page 1387, second column, second full paragraph). Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which block the Il-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S-phase in T-cells (page 336, second column, lines 4-9).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute rapamycin for FK506 in the method of inducing tolerance in an animal as rendered obvious by the combination of references above.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Li et al on the efficacy of using rapamycin in the combined stimulation blockade to produce tolerance and the teachings of Sehgal on the rapamycin:FKBP complex as an inhibitor of TOR. One of skill in the art would recognize that

rapamycin could be substituted for FK506 in the combined costimulation blockade taught by Guibinga et al.

It is noted that none of the provisional applications provide a written description of rapamycin as an agent which inhibits CD4 T-cell signaling consequent to dendritic cell CD+4 engagement., nor is there any written description of a method which utilizes agents which inhibit effective CD4 T cell help as opposed to the physical elimination of CD+4 T cells.

Claims 1-3, 19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alberts et al (Journal of Experimental Medicine, 1998, Vol. 188, pp. 1359-1368) in view of Kurts et al (Journal of Experimental Medicine, 1997, Vol. 186, pp. 239-2450) and Steinman et al (Immunol Rev, 1997, vol. 156, pp. 25-37) and Beschorner (WO 94/05323).

Alberts et al teach that dendritic cells phagocytose apoptotic cells and cross present antigens from the apoptotic cells to cytotoxic T-lymphocytes (abstract). Alberts et al teach that dendritic cells can acquire antigens from tumors, transplants, infected cells and self tissues for stimulation or tolerization of CTLs (abstract), thus fulfilling the specific limitation of claim 19 specifying the types of antigen for which tolerance might be evoked. Alberts et al teach the isolation of dendritic cells from peripheral blood and the use of monocyte conditioned medium (MCM) as a maturation factor for the dendritic cells thus fulfilling the specific embodiments of claim 2 (page 1360, first column, lines 12-14 under the heading of "Preparation of Cells").

Kurts et al (Journal of Experimental Medicine, 1997, Vol. 186, pp. 239-2450 teach that tolerance induced by cross-presented self antigens (versus non-self antigens) relates to a lack of Cd+4 T-cell help which appears to be necessary for the induction of some CD+8 T cell responses (page 243, second column, lines 6-14 of the last paragraph).

Steinman et al (Immunol Rev, 1997, vol. 156, pp. 25-37) teach dendritic cells in the T-cell areas may function to maintain peripheral tolerance to self-antigens by deleting CD+4 t cells via the fas-l mediated pathway (page 33, lines 9-15 of the last paragraph).

Beschorner teaches a method for the induction of antigen specific immune tolerance comprising the depletion of resident thymic antigen presenting cells and re-population of the

thymus with new antigen presenting cells containing the antigen for tolerance (page 8, lines 1-8).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to induce tolerization to self-antigens by presenting apoptotic cells comprising said antigen in the absence of T-cell help and introducing the tolerized dendritic cells back into the mammal in place of the antigen presenting cells of the mammal which were primed against said antigen.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Kurts et al and Steinman et al on the ability of dendritic cells within the t-cell areas to maintain a peripheral tolerance to self antigens by the presentation of said antigens by dendritic cells in the absence of CD+4 T cells as taught by both Kurts et al and Steinman et al. One of skill in the art would also known that it would be necessary to replace the previously sensitized dendritic cells with the dendritic cells which have been tolerized.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is vague and indefinite in the recitation of "a period of time" following step c. The metes and bounds of "a period of time" cannot be determined.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

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02/22/04

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